EXHIBIT A106

Factors Related to Inflammation of the Ovarian Epithelium and Risk of Ovarian Cancer

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Previous epidemiologic observations consistently suggest that suppression of ovulation, tubal ligation, and hysterectomy reduce the risk of ovarian cancer and that perineal talc use increases the risk. We examined these and other risk factors in the context of a new hypothesis: that inflammation may play a role in ovarian cancer risk. Ovulation entails ovarian epithelial inflammation; talc, endometriosis, cysts, and hyperthyroidism may be associated with inflammatory responses of the ovarian epithelium; gynecologic surgery may preclude irritants from reaching the ovaries via ascension from the lower genital tract. We evaluated these risk factors in a population-based case-control study. Cases 20–69 years of age with a recent diagnosis of epithelial ovarian cancer (767) were compared with community controls (1367). We found that a number of reproductive and contraceptive factors that suppress ovulation, including gravidity, breast feeding, and oral contraception, reduced the risk of ovarian cancer. Environmental factors and medical conditions that increased risk included talc use, endometriosis, ovarian cysts, and hyperthyroidism. Gynecologic surgery including hysterectomy and tubal ligation were protective. Tubal ligation afforded a risk reduction even 20 or more years after the surgery. The spectrum of associations provides support for the hypothesis that inflammation may mediate ovarian cancer risk. (Epidemiology 2000;11:111–117)

Keywords: ovarian cancer, endometriosis, oral contraceptives, talc, tubal ligation.

Ovarian cancer is a commonly fatal malignancy for which prevention strategies have been limited, in part, by a lack of understanding of its pathobiology. Factors that have consistently been shown to reduce the risk of ovarian cancer, such as number of pregnancies or live births, contraceptive use, and breast-feeding,[1–5] have been proposed to do so by reducing the number of ovulations or the exposure to high pituitary gonadotrophin levels over a lifetime.[6,7] Nevertheless, the biologic mechanism responsible for other consistently demonstrated protective factors is less well understood; such protective factors include: tubal ligation and hysterectomy,[1,8–18] asbestos[19–21] and talc exposures,[2,22–32] endometriosis,[33–35] and perhaps, pelvic inflammatory disease.[36,37]

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All of these factors may act by a common pathway, by modulating inflammation of the ovarian epithelium, the cell type from which more than 90% of ovarian cancers arise. Ovulation entails disruption of the ovarian epithelium by the extruded follicle, followed by inflammation and wound repair.[38,39] Asbestos, talc, endometriosis, and pelvic inflammatory disease all initiate marked local inflammation. Tubal ligation and hysterectomy sever the pathway from the lower to the upper genital tract, thereby disallowing inflammatory substances to ascend through the lower genital tract to the upper genital tract, and ultimately to the ovarian epithelium.[17] Inflammation involves rapid cell division, DNA excision and repair, oxidative stress, and high concentrations of cytokines and prostaglandins, all of which are established promoters of mutagenesis.[40–43]

Using data from a population-based case-control study of ovarian cancer, we here examine whether factors that are associated with ovarian epithelial inflammation consistently elevate ovarian cancer risk and whether those that reduce the potential for inflammation are protective.

METHODS

Study Subjects

Cases were women 20 through 69 years of age who had had epithelial ovarian cancer diagnosed within the 6 months before the interview. They were ascertained from 39 hospitals around the Delaware Valley including contiguous counties in eastern Pennsylvania, Southern

New Jersey, and Delaware. Between 1994 and 1998, 2,418 cases of histologically confirmed borderline or invasive epithelial ovarian cancer were identified. After excluding women who were not between the ages of 20–69 (640), resided outside the counties in which referral hospitals were located (342), had a prior diagnosis of ovarian cancer (158), or did not speak English or were mentally incompetent (25),[25] we found 1,253 potentially eligible women; after excluding those who were diagnosed more than 6 months before interview (296), were critically ill or dead (69), or were untraceable (15), we were left with 873 women who had incident cancer and were thus eligible for study. Fourteen physicians did not consent to their patients' participation and 92 women refused to participate, resulting in 767 completed case interviews (61% of potentially eligible cases and 88% of potentially eligible, incident cases).

Controls age 65 or younger were ascertained by random digit dialing. These subjects were frequency-matched by 5-year age groups and three-digit telephone exchange to cases. Of the 14,551 telephone numbers screened, 6,597 were businesses or not in service and 5,640 had no female of eligible age in the household, leaving 2,314 households with potentially eligible participants. Of these, 1,928 (83%) had a potentially eligible woman who was willing to be screened further for eligibility. Upon screening, 291 had no eligible woman resident on the basis of age (5), residence outside of the target counties (11), prior diagnosis of ovarian cancer (9), prior bilateral oophorectomy (187), not speaking English or mental incompetence (22), critical illness or death (6), or being untraceable (51). Of the 1,637 screened and potentially eligible controls, 422 declined to be interviewed and 1,215 (74%) were interviewed. Based on our previous experience of lower response rates among 65+ year olds using a random digit dialing approach, we ascertained controls 65–69 years of age through Health Care Financing Administration (HCFA) lists. Four hundred twenty-three women were initially identified, and were frequency-matched to cases by country of residence and age group. One hundred sixty were ineligible for the reasons given above. Of the 263 potentially eligible from HCFA lists, 111 refused to participate and 152 (58%) were interviewed. Therefore, of the total of 1,900 eligible potential controls, 1,367 (72%) are included in these analyses. Age was similarly distributed for cases and controls. Overall, 4% of subjects were age <30, 13% were 30–39, 29% were 40–49, 30% were 50–59, and 24% were 60–69.

Cases included 616 invasive epithelial ovarian cancers and 151 borderline epithelial ovarian tumors. Central pathologic review was conducted on a random sample of 120 cases. The reference pathologist agreed with the original pathologic review for invasiveness in 95% of cases and for cell type in 82% of cases. The original pathologic diagnosis was then used for all cases.

Data Collection

Standardized 1.5-hour interviews were conducted in the homes of participating women by trained interviewers. A life calendar, marked by important happenings that participants recalled during their lives, was used to enhance memory of distant events. On the calendar was coded sexual activity, contraceptives used, and reproductive events for every month from sexual debut until a reference date, defined as the date 6 months before the interview (for both cases and controls).

All pregnancies, their length and outcome as well as the length of breast-feeding, were recorded on the life calendar. The type and length of each contraceptive use was recorded. Tubal ligation, hysterectomy, and ovarian operations were detailed including the time, abdominal *vs* vaginal approach, and procedures done to the ovaries. Menstrual onset, regularity, discomfort, and cessation were recorded. This included questions that asked, "How long did it take before your periods started coming about once a month (without the use of birth control pills)?" and "during your 20's and 30's, and when you were not pregnant, nursing or taking birth control pills/shots/implants, did you ever miss three or more menstrual periods in a row?" The two variables derived from these questions were titled "time to regular menstrual cycles" and "ever miss ≥3 menses." Women were also asked about a series of medical conditions that may be related to pelvic inflammation including ovarian cysts, pelvic inflammatory disease, thyroid disease, and endometriosis. Finally, women were asked about talc use. The question was, "As an adult and prior to [reference date] did you ever use talc, baby or deodorizing powder, at least once per month for 6 or more months on your: 1) feet, arms, or breasts, but not the genital or rectal areas? 2) genital or rectal area? 3) on your sanitary napkins? 4) on your underwear? 5) on your diaphragm or cervical cap?" They were then asked whether they had a male sexual partner(s) for more than a year who regularly used such products on his genital area or underwear. The duration of use of talc for each of these modes of use was also queried.

Statistical Analysis

Because matching was based on frequencies for only two broad criteria, age within 5-year intervals and three-digit telephone exchanges (or county of residence), we did not preserve the "match" in the analyses. We adjusted odds ratios for age and gravidity (each as continuous variables), race (white/black/other), history of ovarian cancer in any first degree relative (yes/no), oral contraceptive use (yes/no), tubal ligation (yes/no), hysterectomy (yes/no), and breast-feeding (yes/no) by unconditional logistic regression analysis.[44]

RESULTS

We first examined reproductive and contraceptive factors that would be expected to affect ovulation and/or endogenous steroid hormones. Pregnancies and breast-feeding were protective for ovarian cancer, with a 50% risk reduction associated with the first pregnancy and a modest additional lowering of risk for pregnancies beyond the first. Breast-feeding reduced risk after at least

TABLE 1. Selected Characteristics Related to Reproductive History and Ovarian Cancer

Variable	Cases (767)	Controls (1367)	Crude OR	95% CI	Adjusted OR*	95% CI
Pregnancies						
0	176	127	1.0		1.0	
1	107	140	0.5	0.4–0.8	0.6	0.4–0.9
2	177	346	0.4	0.3–0.5	0.4	0.3–0.6
3	142	308	0.3	0.2–0.4	0.4	0.3–0.5
4	70	194	0.3	0.2–0.4	0.3	0.2–0.4
≥5	95	252	0.3	0.2–0.4	0.3	0.2–0.4
Oral contraceptive duration (years)						
Never	341	426	1.0		1.0	
<1	141	266	0.7	0.5–0.8	0.8	0.6–1.0
1–4	162	362	0.6	0.4–0.7	0.7	0.6–1.0
5–9	88	189	0.6	0.4–0.8	0.7	0.5–1.0
≥10	32	120	0.3	0.2–0.5	0.4	0.2–0.6
Breast-fed (months)†						
Never	299	577	1.0		1.0	
1–5	117	259	0.9	0.7–1.1	0.9	0.7–1.2
6–11	46	119	0.9	0.5–1.1	0.9	0.6–1.3
12–23	40	124	0.6	0.4–0.9	0.7	0.5–1.1
≥24	29	111	0.5	0.3–0.8	0.6	0.4–1.0
Age at menarche (years)						
≤11	171	316	1.0		1.0	
12	205	382	1.0	0.7–1.3	1.0	0.8–1.3
13	203	341	1.0	0.8–1.3	1.0	0.8–1.4
≥14	188	328	1.0	0.8–1.3	1.0	0.8–1.3
Age at natural menopause (years)‡						
<45	108	186	1.0		1.0	
45–49	122	183	1.1	0.8–1.6	0.9	0.6–1.4
50–52	84	123	1.2	0.8–1.7	0.9	0.6–1.4
≥53	53	74	1.2	0.8–1.9	1.0	0.6–1.6
Length of menstrual cycles (days)						
26–34	599	1044	1.0		1.0	
≤25	82	139	1.0	0.8–1.4	1.1	0.8–1.5
≥35	25	54	0.8	0.5–1.3	0.8	0.5–1.4
Never regular	47	93	0.9	0.6–1.3	1.0	0.7–1.4
Time to regular menstrual cycles (months)						
1	480	898	1.0		1.0	
2–6	143	208	1.3	1.0–1.6	1.3	1.0–1.7
7–12	53	102	1.0	0.7–1.4	1.1	0.8–1.6
≥13	65	125	1.0	0.7–1.3	1.0	0.7–1.5
Ever miss ≥3 menses						
No	719	1293	1.0		1.0	
Yes	41	64	1.2	0.8–1.7	1.2	0.8–1.8

* Adjusted for age, number of pregnancies, family history of ovarian cancer, race, oral contraceptive use, tubal ligation, hysterectomy, and breast-feeding.
† Among women who had had a live birth.
‡ Excludes women who were pre-menopausal, had had a hysterectomy, or were using hormone replacement therapy prior to the cessation of menses.

24 months of breast-feeding over a lifetime (Table 1). Oral contraception provided a duration-dependent reduction in risk. Neither age at menarche nor age at natural menopause was strongly associated with ovarian cancer risk. Similarly, menstrual patterns had little association with ovarian cancer risk. In particular, never having regular menstrual cycles, which may be a marker of anovulation, did not substantially lower ovarian cancer risk.

We next evaluated environmental factors and medical conditions that might be associated with increased local inflammation (Table 2). Talc use on all areas of the body elevated ovarian cancer risk, even after adjustment for potentially important confounding factors. Similarly, talc use on sanitary napkins and underwear elevated ovarian cancer risk. In contrast, talc use on diaphragms and/or cervical caps and use by the male partner did not appear to alter risk by much. Furthermore, length of use was not clearly related to risk.

Three medical conditions increased ovarian cancer risk in our data: ovarian cysts (adjusted OR 1.3), endometriosis (adjusted OR 1.7), and hyperthyroidism (adjusted OR 1.8). The relation between these medical conditions and ovarian cancer appeared to be relatively specific. We did not, for example, find associations between ovarian cancer and lower genital tract infections that do not cause ovarian inflammation, such as genital warts and herpes simplex infection (data not shown). Nevertheless, pelvic inflammatory disease, which does cause ovarian inflammation, was only modestly associated with ovarian cancer in our data.

Gynecologic surgery, including tubal ligation and hysterectomy, reduced ovarian cancer risk (Table 3). Tubal ligation and tubal ligation in combination with hysterectomy both provided marked protection (odds ratios 0.5 and 0.4). Hysterectomy without tubal ligation was less protective (odds ratio 0.8). To examine the possibility that surveillance bias, that is removal of an unusual appearing ovary destined to become cancer, may have accounted for these relations, we evaluated the association between time since gynecologic surgery and ovarian cancer risk. Although there was a trend toward

TABLE 2. Environmental Factors and Medical Conditions and Ovarian Cancer

Variable	Cases 767	Controls 1367	Crude OR	95% CI	Adjusted OR*	95% CI
Talc use†						
Never	349	728	1.0		1.0	
Feet, etc	335	512	1.4	1.1 –1.6	1.4	1.1–1.6
Genital/rectal	161	219	1.5	1.2 –1.9	1.5	1.1–2.0
Sanitary napkin	77	94	1.7	1.2 –1.9	1.6	1.1–2.3
Underwear	70	100	1.5	1.0 –2.0	1.7	1.2–2.4
Diaphragm/Cerv Cap	10	33	0.6	0.3 –1.3	0.6	0.3–1.2
Male partner	56	126	0.9	0.7 –1.3	1.0	0.7–1.4
Talc use (genital/rectal and feet)						
Never	401	819	1.0		1.0	
<1 year	17	17	2.0	1.0 –4.0	2.0	1.0–4.0
1–4 years	76	101	1.5	1.1 –2.1	1.6	1.1–2.3
5–9 years	40	59	1.4	0.9 –2.1	1.2	0.8–1.9
10+ years	233	371	1.3	1.0 –1.6	1.2	1.0–1.5
Ovarian cysts						
No	604	1131	1.0		1.0	
Yes	154	231	1.2	1.0 –1.6	1.3	1.1–1.7
Thyroid disease						
Never	646	1165	1.0		1.0	
Overactive	30	30	1.8	1.1 –3.0	1.8	1.0–3.0
Underactive	72	138	0.9	0.7 –1.3	0.9	0.6–1.2
Endometriosis						
No	698	1279	1.0		1.0	
Yes	66	85	1.5	1.0 –2.1	1.7	1.2–2.4
Pelvic inflammatory disease						
No	752	1335	1.0		1.0	
Yes	14	27	0.9	0.5 –1.8	1.3	0.6–2.5

* Adjusted for age, number of pregnancies, family history of ovarian cancer, race, oral contraceptive use, tubal ligation, hysterectomy, and breast-feeding.
† Subjects may have used talc on more than one area of the body so numbers add to more than 767 cases and 1,367 controls.

less protection with a longer period of time since tubal ligation, risk reduction was still afforded to women with that surgery 20 or more years earlier. Abdominal hysterectomy, which affords a direct view of the abdominal cavity, was not more protective than vaginal hysterectomy, which does not afford a direct view, making it unlikely that removal of an abnormal-appearing ovary at surgery accounted for the protection afforded by gynecologic operations. Laparoscopy for reasons other than tubal ligation or ovarian operations, which would also allow a surgeon to inspect the ovaries and remove any

TABLE 3. Gynecologic Surgery and Ovarian Cancer

Variable	Cases (767)	Controls (1367)	Crude OR	95% CI	Adjusted OR*	95% CI
Neither	570	797	1.0			
Tubal ligation	117	388	0.4	0.3–0.5	0.5	0.4–0.7
Hysterectomy	67	118	0.8	0.6–1.1	0.8	0.6–1.1
Both	13	63	0.3	0.2–0.5	0.4	0.2–0.8
Time since tubal ligation (years)						
Never	637	915	1.0			
<2	3	20	0.2	0.1–0.7	0.3	0.1–1.1
2–9	21	80	0.4	0.2–0.6	0.6	0.4–1.0
10–19	53	194	0.4	0.3–0.5	0.5	0.3–0.7
≥20	53	155	0.5	0.4–0.7	0.6	0.4–0.9
Time since hysterectomy						
Never	687	1186	1.0			
<2	2	4	0.9	0.2–4.7	1.0	0.2–6.3
2–9	14	39	0.6	0.3–1.2	0.9	0.5–1.6
10–19	25	68	0.6	0.4–1.0	0.7	0.4–1.2
≥20	39	69	1.0	0.7–1.5	0.8	0.5–1.3
Type of hysterectomy						
Never	687	1186	1.0			
Abdominal	60	113	0.9	0.7–1.3	0.9	0.6–1.3
Vaginal	20	66	0.5	0.3–0.9	0.6	0.3–1.0
Laparoscopy						
Never	711	1264	1.0			
Ever	55	102	1.0	0.7–1.3	1.0	0.7–1.5

* Adjusted for age, number of pregnancies, family history of ovarian cancer, race, oral contraceptive use, and breast-feeding.

that were abnormal, did not affect the risk of ovarian cancer substantially.

DISCUSSION

These analyses are generally, albeit not completely, consistent with the hypothesis that inflammation at the site of the ovarian epithelium is associated with ovarian cancer risk. Our results confirmed the findings of a number of previous studies showing that pregnancies, oral contraceptive use, and prolonged breast feeding, reduce the risk of ovarian cancer.[1–5] All of these factors mark a diminution in number of ovulations and a reduction in pituitary gonadotrophin levels (during breastfeeding, LH levels are suppressed, but FSH levels are not).[45] We did not find, however, that markers of the length of the reproductive window, such as age at menarche, age at natural menopause, and the regularity of menses, were substantially related to ovarian cancer risk. These factors have been inconsistently and/or weakly related to risk in previous studies,[46] perhaps because they inaccurately reflect ovulatory function. The initiation and cessation of menses do not correlate well with the initiation and cessation of ovulation, whereas pregnancy and oral contraceptive use more validly reflect termination of ovulation.[5,47,48]

We found that several factors, which may reflect an inflammatory process at the site of the ovarian epithelium, increase the risk for ovarian cancer. Talc use applied to any part of the body or to sanitary napkins or underwear was related to ovarian cancer risk. These observations are consistent with findings from several previous studies.[2,22–32] Of the 12 epidemiologic studies that we identified that have evaluated the use of talc in relations to ovarian cancer,[2,22–32] 10 have reported at least some elevation in cancer risk among women. In the most extensive and focused analysis to date, Cook *et al.*[22] analyzed data from 313 cases of ovarian cancer and 422 controls regarding recalled use of talc products.[22] Use in the perineal area, powder on sanitary napkins, and genital deodorant spraying were all associated with elevated ovarian cancer risk, whereas, as in our study, use on a diaphragm was not. We found, however, that a small number of women used powder on their diaphragm, thereby limiting the interpretation of these data. The lack of specificity for the body part on which talc was used may be related to the fact that small particles of talc often become airborne during use so that a broader area of the body may be exposed than that to which the talc was directly applied. Some previous studies have found dose-response or duration-response relations between talc use and ovarian cancer,[24,27] whereas others have not.[2,22,31] The reasons for this are unclear.

Endometriosis, the presence of endometrial tissue outside the endometrium, causes a marked local inflammatory reaction. It has been linked to ovarian cancer in a variety of epidemiologic and clinical studies.[33–35,49] Brinton *et al.* assessed cancer outcomes among over 20,000 women hospitalized for endometriosis in Sweden after a mean of 11 years of follow-up.[49] Ovarian cancer risk was elevated as much as fourfold for women whose endometriosis arose in the ovaries. A series of clinical studies have also demonstrated ovarian malignancies arising from ovarian endometriosis, that is, from endometriosis that resides in the ovarian epithelium.[33–35]

Finally, although the link between simple ovarian cysts and ovarian cancer is not clearly established, complex cysts, which may have neoplastic or physiologic components and involve marked local inflammation, may be precursor lesions for ovarian cancer. In our study, we could not distinguish between types of cysts inasmuch as our data were based on self-report. A previous case-control study, which also did not distinguish between pathologic sub-types, found that ovarian cysts were associated with a 12-fold increased risk of ovarian cancer.[36]

The association between hyperthyroidism and ovarian cancer is a novel observation, to our knowledge, and may provide an important clue to our hypothesis. The most common cause of hyperthyroidism is autoimmune inflammation of the thyroid gland.[50] Autoimmune hyperthyroidism, including Graves' disease and Hashimoto's thyroiditis, involve both humorally mediated and cellular immune responses directed against thyroid microsomes, thyroglobulin, and thyroid antigen.[51] They are much more common in women than in men. These diseases run in families in which there are higher rates of other autoimmune disorders, including insulin-dependent diabetes mellitus, rheumatoid arthritis, and systemic lupus erythematosus. Autoimmune diseases in general, and autoimmune thyroid disorder in particular, are systemic, causing inflammation and infiltration beyond the thyroid (*eg* infiltrative ophthalmopathy and dermopathy in Graves disease). There are a variety of reproductive manifestations of hyperthyroidism that have been attributed to thyroid hormonal influences on steroid hormone metabolism.[52] Fertility is impaired, however, even in women with ovulatory cycles, and it is possible that a local inflammatory process may be involved, although to our knowledge, this has never been studied. It would have been interesting to have examined the relations between other autoimmune diseases and ovarian cancer, but, we did not ask about other autoimmune diseases in this study.

We found only a modest elevation in risk associated with pelvic inflammatory disease, whereas the association has been more clearly shown in some previous studies.[36,37] In our study, however, only about 2% of cases and of controls reported previous pelvic inflammatory disease and the power to detect the association was limited. In contrast, national surveys have suggested that 10% or more of American women report this condition during their reproductive lives.[53] This discrepancy suggests the possibility that our study participants substantially under-reported pelvic inflammatory disease (which, because of its links to sexually transmitted diseases, is more socially sensitive than other exposures queried in this study) and may account for the lack of a clearer study finding.

Our data and data from previous studies[1,8–18] suggest that gynecologic surgery, in particular tubal ligation, greatly reduce the risk of ovarian cancer. The following observations, taken as a whole, argue against a surveillance bias whereby abnormal ovaries are removed at the time of surgery: (1) ovarian cancer risk is reduced 20 or more years after tubal ligation; (2) vaginal hysterectomy, which is accomplished without observation of the ovaries, is not less protective than abdominal hysterectomy, wherein ovaries are observed; and (3) laparoscopy does not lower risk. We believe that the protection afforded by gynecologic surgery, and, in particular by tubal ligation, which is generally accomplished earlier in life, is mediated by disrupting the connection between the ovaries and the rest of the genital tract structures.[17] Substances that may cause lower genital tract inflammation, such as talc, can travel up an open genital tract, but with tubal ligation or hysterectomy, that pathway is cut-off, thereby reducing the risk of environmentally mediated inflammation.

Inflammation by its nature produces toxic oxidants meant to kill pathogens. These oxidants cause direct damage to DNA, and it has been proposed that oxidative damage to DNA underlies all mutagenesis. In particular, Ames *et al.* argue that damage to critical tumor suppressor genes, particularly in the situation of rapid cell division, as is found in inflammation, contributes to cancer development.[40] Furthermore, bioactive substances, such as cytokines, growth factors, and prostaglandins, which are part of the inflammatory process, may play a role in ovarian mutagenesis.[41–43] Disregulated cytokines may lead to ovarian neoplasm progression, and overexpression of prostaglandins, which is more common in tumor cells, increases tumor invasiveness.[54]

A limitation of our study was the somewhat low participation rates among cases and controls. For cases, this factor was strongly influenced by whether women with prevalent ovarian cancer (diagnosed >6 months before interview) were included in the denominator when calculating response rates. In our design, we excluded such women to avoid survival bias. Excluding them from the denominator resulted in an 88% response rate; however, to the extent that exposures may differ in women with incident ovarian cancer from those with ovarian cancer overall, we report the 61% response rate with them included in the denominator. Another limitation of our study is the potential for recall bias, which is a concern with any case-control study. In our study, however, recall bias is unlikely to explain factors that appear to be protective, which was the case for many of the associations found. As well, medical risk factors were not universally associated with elevated risk, but, instead the associated factors appeared to be specifically those causing inflammation. A final limitation is that many of our effect sizes were modest.

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